REMARKS

Claims 1-3, 6, 8, 14-17 and 19-37 are pending and under examination. No claim has been added, canceled or amended herein. Accordingly, claims 1-3, 6, 8, 14-17 and 19-37 are still pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's objections and rejections made in the February 19, 2002 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides a small molecular weight tumor necrosis factor receptor molecule and related methods. This receptor molecule binds TNF and comprises all or a functional portion of at least two extracellular domains of TNF receptors linked via one or more polypeptide linkers. The polypeptide linkers are from about 10 to about 30 amino acids in length.

The claimed receptor molecule shows *surprising* advantages over other multi-TNF receptor-based molecules. Specifically, the instant molecule, as exemplified by Hu TNF-R75 ECD, shows the same anti-TNF-specific activity as an Ig-based TNF receptor molecule - and at *only a third of the concentration* required for the Ig-based molecule. Even more dramatic is the fact that a concentration of TNF receptor monomer 300-fold higher than that tested for the instant molecule *was ineffective*.

The claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-3, 6, 8, 14-17 and 19-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Wallach, et al. (U.S. Patent No. 5,478,925, "Wallach I") or Wallach, et al. (EP 0 526 905, "Wallach II").

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants incorporate herein by reference their remarks made in the October 15, 2001 Amendment.

Claims 1-3, 6, 8, 14-17 and 19-37 provide a small molecular weight TNF receptor-based molecule and methods of using same. This molecule binds TNF and comprises all or a functional portion of two extracellular domains of TNF receptors linked via one or more polypeptide linkers of 10-30 amino acids in length.

As stated already, the claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must be a reasonable expectation that the claimed invention would succeed.

Here, each of the cited references fails to support a *prima facie* case of obviousness. To support a *prima facie* case of obviousness, each of Wallach I or Wallach II, in view of routine skill in the art, would at a minimum have to teach or suggest every element of the claims.

Neither Wallach I nor Wallach II does this.

Specifically, each reference teaches TNF receptor multimers. These multimers are made from monomers held together by *any* means (see Wallach II, page 2, lines 44-46). For example, the monomers may be held together by both covalent bonding, such as via chemical cross-linkers, as well as non-covalent bonding, such as via liposome formation. As stated in the previous response, joining monomers covalently via a peptide linker is but only one method out of a veritable universe of possibilities taught by the references.

According to the Examiner, it can be "reasonably interpreted by the skilled artisan that Wallach et al. teaches that...the [linker] length for optimum activity...can be determined experimentally by one of ordinary skill in the art". At most, the *possibility* that one skilled in the art could have optimized a linker length using

routine experimentation is merely an invitation to experiment further. Such a possibility, as taught by the art, does not constitute the teaching of the linker length, i.e., 10-30 residues, which applicants actually conceived. Thus, the cited references fail to teach or suggest all elements of the rejected claims.

Applicants also wish to comment on certain other statements made by the Examiner. First, the Examiner states that based on the molecular weights of the two dimers (i.e., Hu p75 TNF-R ECD dimer and Hu p75 TNF-R ECD dimer in an IgG backbone), "the claimed molecule does not seem to have a significantly greater activity" than that of the dimer in an IgG backbone. Applicants note that the Examiner's position, whether or not correct, is inapposite to the non-obviousness of the claimed molecule. That is, assuming solely for the sake of argument that the binding activities are the same for each multimer, it is still surprising that the instant multimer has such a property while being much smaller and having a polypeptide linker of 10-30 residues in length. Second, contrary to the Examiner's position, it is not necessary that applicants show that an Ig Fc domain *would* in fact cause side effects in a subject if present on a TNF-binding multimer. Rather, the absence of an Fc domain having the potential to cause side effects, i.e., an immune response, is itself an advantage of the instant molecules. In this regard, applicants direct the Examiner to the specification (page 12, lines 18-21), which states that "the Ig fusion proteins are expected to bind complement to the Fc receptor of a cell surface thereby facilitating development of an immune response. In contrast, the receptors of the present invention, being devoid of an Ig structure, are not expected to be immunogenic". Indeed, for the reasons already discussed, the

unexpected binding properties of the instant molecules do not rely on the function, or expected function, of the Fc domain.

In light of these references and their shortcomings, the Examiner has failed to show how either cited reference teaches or suggests every element of the claims, or provides a reasonable expectation of success for the claimed invention. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 14-17 and 19-37 over Wallach I or II, in view of routine skill in the art at the time of the invention.

The Examiner also rejected claims 1-3, 6, 8, 14-17 and 19-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Smith, et al. (U.S. Patent No. 5,395,760).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The rejected claims are discussed above.

Smith, et al. teach that "both monovalent and polyvalent forms of TNF-R are useful in the compositions and methods of the invention...[f]or example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of FIG. 2A, separated by a linker region" (see column 10, lines 33-39). Smith, et al. do not define the optimal length of this linker region. Instead, Smith,

et al. focus on providing examples of polyvalent forms of TNF-R constructed by chemical coupling techniques. In essence, Smith, et al. suffer the same deficiency seen in Wallach I and II, i.e., they teach a receptor-based molecule with a virtually infinite number of linker permutations. In combination with routine skill in the art, Smith, et al. cannot be construed to teach or suggest a receptor-based molecule comprising a *peptide* linker of a *defined* length, i.e., 10-30 residues, as in the claimed invention. Thus, this reference, in combination with routine skill, fails to teach or suggest all elements of the rejected claims, and fails to provide a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 14-17 and 19-37 over Smith, et al., in view of routine skill in the art at the time of the invention.

In view of the above remarks, applicants maintain that claims 1-3, 6, 8, 14-17 and 19-37 satisfy the requirements of 35 U.S.C. §103(a).

Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number

provided below.

No fee, other than the $920.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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8/19/02
Alan J. Morrison Date
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